REMARKS

Applicant respectfully requests reconsideration and allowance of all pending claims.

I. Status of the Claims

Upon entry of this Amendment C, claims 1-23 remain pending in this application.

Independent claims 1, 9, 14, and 19 have been amended herein to more particularly claim certain embodiments. In particular, these claims have been amended to indicate the claimed storage stable solution is an oral solution; that is, the claimed storage stable solution is designed for oral administration. Support for the amendments to these claims can be found in the instant Specification at, for example, paragraphs [0003-4], [0009], [0011], and [0013-16].

II. 35 U.S.C. 103(a) Rejection

For the reasons set forth in detail below, as well as for the reasons set forth in Applicant's previous submissions (including Amendments A and B, which in the interests of brevity will not be repeated here), Applicant respectfully requests reconsideration of the rejection of claims 1-23 under 35 U.S.C. §103 as being obvious in view of the combination of Midha et al. (U.S. Patent No. 6,127,385) and Epstein et al. (U.S. Patent Publication No. 2002/0103162).

A. The Claimed Subject Matter

The present application is directed to an **oral** methylphenidate solution (e.g., a solution of the free base or a pharmaceutically acceptable salt thereof) that has improved chemical stability, and therefore improved shelf-life or **storage stability** as well. (See, e.g., paragraphs [0001] and [0010].) Applicant has discovered that by preparing an **oral** solution of methylphenidate using a solvent system comprising a combination of water and a non-aqueous solvent, and in particular an aqueous **solvent system** comprising **less than about 50% water** (or alternatively **greater than about 50% of the non-aqueous solvent**), the chemical stability, and therefore the shelf-life or storage stability, of the solution is improved. (See, e.g., paragraphs [0008] and [00010].) As illustrated in Applicant's working examples, such oral solutions have been observed to have an improved shelf-life or storage stability, including a projected shelf-life of at least two years. (See, e.g., paragraph [00021] and Examples 1-3.)

Additionally, Applicant has discovered that such oral solutions strike an effective balance between **storage stability** and **taste**, which is an important consideration for **oral** solutions, particularly those designed for pediatric use. (See, e.g., paragraphs [0011] and [0013-16].)

B. The Cited Art

Midha et al. disclose a method of treating depression in a patient by oral or non-oral administration of the active 1-threo-methylphenidate, which may be in the form of the free base or a pharmaceutically acceptable salt. (See, e.g., column 1, lines 5-8, and column 2, lines 36-38). Although they make a general reference to a solution containing the active, ascorbic acid, and an aqueous or non-aqueous solvent (see, e.g., column 4, lines 59-63), they **fail to disclose or suggest** a **storage stable** solution comprising the active in a **solvent system** that in turn comprises both water and a non-aqueous solvent, **wherein the concentration of water therein is less than about 50%**.

Furthermore, it is to be noted that Midha et al. **do not make any specific reference at all** to the concentration of water, or the concentration of the non-aqueous solvent, in a solution that contains both in combination with the active. Applicant respectfully submits this is because Midha et al. are simply not concerned with the storage stability or shelf-life of such a solution. Evidence of this may be found in the fact that they **do not even reference storage stability** or shelf-life as factors to be considered when preparing such a solution. Rather, they are simply interested in the **administration** of their solutions or compositions.

Epstein et al. disclose methods and compositions for enhancing long-term memory function and/or performance. (See, e.g., paragraph [0006].) Although they make a general reference to the preparation of a solution of a methylphenidate compound using, among other things, water, a polyol or a mixture thereof (see, e.g., paragraph [0250]) as a solvent, like Midha et al., they also fail to disclose or suggest a **storage stable** solution comprising the active in a **solvent system** that in turn comprises both water and a non-aqueous solvent, **wherein the concentration of water therein is less than about 50%**.

Furthermore, it is to be noted that Epstein et al. **do not make any specific reference at all** to the concentration of water, or the concentration of the non-aqueous solvent, in a solution that contains both in combination with the active. Applicant respectfully submits this is because Epstein et al., like Midha et al, are simply not concerned about the storage stability or shelf-life of such a solution. Evidence of this may be found in the fact that **they do not even reference**

storage stability or shelf-life as factors to be considered when preparing such a solution. Rather, they too are simply interested in the **administration** of their solutions or compositions.

As noted in Applicant's Letter to the Patent Office (dated February 5, 2008), the above-noted interpretations of the Midha et al. and Epstein et al. references are supported by the declaration of Clifford J. Herman (also dated February 5, 2008). In his declaration, Mr. Herman states that a completely aqueous solvent system (or even a solvent system that includes greater than about 50% water) is not suitable for a methylphenidate solution, due to problems with solubility and storage stability. Mr. Herman also states he discovered that, in order to preserve the storage stability of the methylphenidate solution, the solution needs to comprise less than about 50% water (or alternatively, greater than about 50% of a non-aqueous solvent). Furthermore, **Mr. Herman states that both of the cited references fail to recognize or acknowledge that methylphenidate solutions are inherently unstable**, and that none of the solutions or compositions disclosed in the working Examples or described anywhere else therein comprise less than about 50% water (or alternatively, greater than about 50% of the non-aqueous solvent). As a result, there is no reason to believe that any of the solutions prepared in the cited references are storage stable.

Additionally, with regard to dependent claim 2 and independent claims 9, 14, and 19, **Mr. Herman states that the cited references also fail to recognize the benefit of including the recited concentrations of an organic acid in the methylphenidate solution, in order to further stabilize the solution**. Specifically, as noted in the declaration by Mr. Herman, the addition of an organic acid (e.g., citric acid) to the methylphenidate solution at the recited concentration (e.g., a concentration of from about 0.5 mg/ml to about 5.0 mg/ml) enables better control of the pH of the methylphenidate solution, which further stabilizes the solution. While Epstein et al. list citric acid as a metal chelating agent (see, e.g., U.S. Patent Application Publication No. 2002/0103162 at paragraph [0274]), there is no suggestion in the cited reference of using citric acid, or any other organic acid, as a stabilizing agent. Furthermore, there is no suggestion to use an organic acid in the amounts recited in Applicant's claims 2, 9, 14 and 19.

C. The Claimed Subject Matter is Not Obvious

As set forth in M.P.E.P. §2143, in order for the Office to establish a *prima facie* case of obviousness, there must be a clear articulation of the reasons why the claimed invention would have been obvious.; that is, the Office must articulate: (1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge

generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings to arrive at each and every limitation of the claimed invention; (2) a finding that there was reasonable expectation of success; and (3) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness. Applicant respectfully submits the Office has failed to establish a *prima facie* case of obviousness, because (i) each and every element of the claims has not been disclosed or suggested, and/or (ii) motivation is simply not provided to prepare the claimed storage stable methylphenidate solution.

Applicant submits that Midha et al. and Epstein et al., both alone and in combination, fail to disclose or suggest a storage stable solution **designed for oral administration** comprising, among other things, methylphenidate, or methylphenidate HCl, and an aqueous solvent system that has a water concentration of less than 50%. More specifically, the combination of Midha et al. and Epstein et al. fail to disclose an **oral, storage stable solution** comprising such an aqueous solvent system, wherein:

(i) the water concentration is between about 10% and about 45% and the non-aqueous solvent concentration is at least about 50% (Claim 1);

(ii) the water concentration is less than about 50%, the polyol concentration is between about 30% and about 70%, and the glycol concentration is between about 10% and about 70% (Claim 9);

(iii) the water concentration is between about 10% and about 45%, the polyol concentration is between about 40% and about 60%, and the glycol concentration is between about 10% and about 30% (Claim 14); or,

(iv) the water concentration is between about 30% and about 40%, the polyol concentration is between about 45% and about 55%, and the glycol concentration is between about 10% and about 20% (Claim 19).

Notably, both Midha et al. and Epstein et al. **fail to disclose or suggest any specific details** relating to an **oral, storage stable solution** comprising methylphenidate as the active in combination with water and another non-aqueous solvent; that is, neither reference provides

details of the water content or the non-aqueous solvent content in a solution **designed for oral administration**.

Applicant also submits that there is simply **no reason or motivation** for one of ordinary skill in the art to modify the disclosures of Midha et al. and Epstein et al. in order to prepare a storage stable solution **designed for oral administration** comprising a solvent system as recited in any one of claims 1, 9, 14 or 19, because **neither Midha et al. nor Epstein et al. provide any link between the solutions they generally reference and the storage stability or shelf-life thereof**. In fact, as previously noted above, they do not even identify storage stability or shelf-life as a factor to be considered when preparing a solution designed for oral administration.

Applicant notes the Office once again asserts, citing *In re Aller* (105 USPQ 233, 235 (CCPA 1955)), that:

> it is obvious to vary and/or optimize the amounts . . . of aqueous and non-aqueous solvents . . ., **according to the guidance provided** by Midha et al. and Epstein et al. to provide a composition having the desired properties such as the desired concentrations and percentages of each component to formulate an effective methylphenidate solution **for administration**. (See the Office action at the bottom of page 4/top of page 5. Emphasis added.)

However, Applicant respectfully submits that providing guidance for preparation of a solution of methylphenidate for "administration" is not the issue here. Rather, the issue is providing **motivation** to prepare a solution **designed for oral administration** that has improved storage stability and shelf-life, and thus has the composition as claimed. As noted in MPEP §2144.05(II)(B), **a particular parameter must first be recognized as a result-effective variable** before the determination of the optimum or workable ranges of the parameter might be characterized as routine experimentation. (Citing *In re Antonie*, 195 USPQ 6 (CCPA 1977).) Notably, **neither Midha et al. nor Epstein et al. make such a recognition.** More specifically, nowhere in either reference is the storage stability and shelf-life of an oral methylphenidate solution even mentioned.

Furthermore, as noted in Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd., the Federal Circuit has stated that "in cases involving new chemical compounds, **it remains necessary to identify some reason that would have led a chemist to modify** a known compound in a particular manner to establish *prima facie* obviousness of a new claimed

compound."[1] The same is true here, with respect to the claimed solution. Therefore, the Office has provided no more than an "obvious to try" reason; specifically, that the compositions of Midha et al. and Epstein et al. would be modified to have "the desired properties such as the desired concentrations and percentages of each component to formulate an effective methylphenidate solution for administration." (See the current Office action at pages 4-5.) Nowhere, however, is a reason specifically articulated as to why one skilled in the art would modify the **amount of water and/or non-aqueous solvent** to produce the desired **storage stable** solution for **oral** administration. As such, Applicant respectfully submits Midha et al. and Epstein et al. fail to provide a reason or the guidance, and therefore the motivation, to prepare an oral, storage stable solution having the concentrations of aqueous and non-aqueous solvents in the ranges as required in any one of Applicant's claims 1, 9, 14 or 19.

Finally, Applicant respectfully submits the Office has failed to properly or fully consider the declaration previously submitted by Applicant (i.e., the declaration by Mr. Herman dated February 5, 2008 referenced above), in a manner consistent with the requirements of MPEP §716.01. The Office's repeated rejections of the present claims consistently hinge on the position that one of ordinary skill in the art would find motivation to modify the disclosure of the cited references, and in particular the water content of any solvent system disclosed therein, in order to arrive at the claimed subject matter. However, the Office fails to comment at all on the assertions made in the declaration by Mr. Herman, as one of ordinary skill in the art, that (1) neither of the cited references acknowledge that methylphenidate solutions are unstable, and therefore (2) neither of the cited references provide motivation to modify the solutions disclosed therein in order to improve stability.

In view of the foregoing, Applicant respectfully submits that the Office has failed to meet its burden in establishing a *prima facie* case of obviousness here, because each and every element of the claimed storage stable solution has not been disclosed or suggested by the combination of Midha et al. and Epstein et al., and/or because motivation is simply not provided by the combination of Midha et al. and Epstein et al. to prepare a storage stable solution as claimed. Therefore, reconsideration of the rejection of claim 1-23 is respectfully requested.

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[1] 492 F.3d 1350, 1357 (Fed. Cir. 2007). (Emphasis Added.)

CONCLUSION

In view of the foregoing, Applicant respectfully requests favorable reconsideration and allowance of all pending claims.

The Commissioner is hereby authorized to charge Deposit Account 13-1160 for any fees due for the submission of this Amendment C, including a two (2) month extension of time.

Respectfully submitted,

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